Leukaemia Diagnosis Interpretation
All Participants

Participant: 42981 **Trial No: 151604**

Date Issued: 04-January-2016 **Closing Date: 22-January-2016**

Trial Comments

This was an electronic only trial issued to a total of 763 participants. This version replaces version 1.0.0 which contains a scoring error

Your Diagnosis: AML with t(9;11)(p22;q23);MLLT3-MLL

Consensus Diagnosis: B lymphoblastic leukaemia/lymphoma, with t(v;11q23); MLL rearranged

Your Diagnosis is classed as a **MAJOR ERROR** result

Performance Score: 50

Running Score: 100

Consensus

	Consensus Diagnosis	Your Diagnosis
Lineage	Lymphoid-B cell	Myeloid Neoplasms
Subclassification	Precursor B-cell neoplasm	Acute myeloid leukemias (AMLs) and related precursor n
Diagnosis	B lymphoblastic leukaemia/lymphoma, with t(v;11q23); MLL rearranged	AML with t(9;11)(p22;q23);MLLT3-MLL

Breakdown of returned diagnoses

Diagnosis	No Of Returns	Percentage Of Returns
Total Returns	299	100.0
B lymphoblastic leukaemia/lymphoma, with t(v;11q23); MLL rearranged	252	84.2
Mixed phenotype acute leukaemia with t(v;11q23);MLL rearrangement	20	6.7
Acute undifferentiated leukaemia	18	6.0
AML with t(9;11)(p22;q23);MLLT3-MLL	5	1.7
AML without maturation	1	0.3
Lymphocyte-rich classical Hodgkin lymphoma	1	0.3
Therapy-related myeloid neoplasms	1	0.3
B lymphoblastic leukaemia/lymphoma, NOS	1	0.3

Conclusion

Sheffield Teaching Hospitals NHS Foundation Trust, a UKAS proficiency testing provider No. 7804, operating UK NEQAS for Leucocyte Immunophenotyping.

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Leukaemia Diagnostic Interpretation trial 151604

Case History

A 58 year old male presented with relapse of disease

Haematological examination revealed the following:

Hb- 56 g/L; WBC- 153.94 x10^9/L; PLT- 34 x10^9/L; RBC- 1.85 x10^12/L; HCT- 0.169 L/L; MCV- 91.4 fL; MCH- 30.3 pg

Immunophenotype

The consensus results of the malignant cells had the following phenotype (consensus percentage expression in brackets rounded to the nearest whole percentage).

Positive antigens – CD15 (64%), CD38 (94%), CD45 (100%), HLADR (98%)

PLEASE NOTE

Results from the referring centre - cCD79a (87%), TDT (83%)

Negative antigens – CD2 (0%), CD3 (0%), cCD3 (0%), CD5 (0%), CD7 (0%), CD10 (0%), CD13 (1%), CD19 (16%), CD20 (0%), CD22 (6%), CD33 (1%), CD34 (1%), CD56 (0%), CD79a (0%), CD117 (0%), Myeloperoxidase (1%), TDT (2%)

Cytogenetics and Molecular genetics

FISH analysis of 100 interphase nuclei has shown the KMT2A (previously known as MLL) rearrangement at 11q23

Peripheral Blood Morphology

Morphology comments from Professor Wendy Erber
Consultant Haematologist, University of Western Australia, Nedlands, Australia

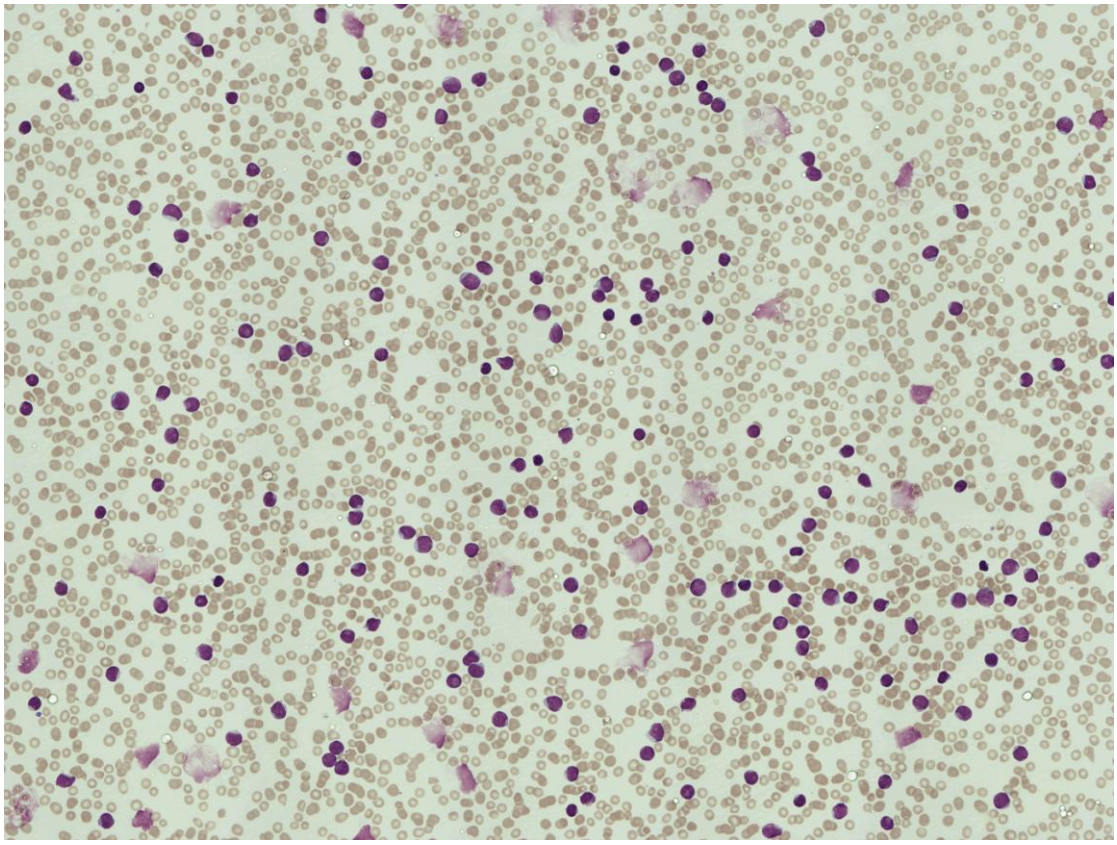
COMMENT:

There is a peripheral blood leucocytosis of small blast cells. These have a high nuclear:cytoplasmic ratio and monomorphic immature chromatin. Many of the blast cells have a nuclear cleft. Neutropenia and thrombocytopenia are noted.

Diagnosis: Morphology of lymphoblastic leukaemia/lymphoma.

Examples of Digital Images Issued

Figure 1: Peripheral Blood x50 magnification (May Grünwald Giesma stain)



Exercise Conclusion / Case Discussion

Please note that, because this trial requires a diagnosis based on the WHO guidelines, this report is therefore based on the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th Edition[2].

Leukaemia Immunophenotyping - Part one

On this send out there were no major issues with respect to manufacturer or fluorochrome variations seen.

We have undertaken further analysis of the data returns in view of the fact that the case was deemed to be positive for TdT and CD79a at the referring centre but was not considered positive when the overall consensus was determined (hence providing this additional information in Part 2 that would aid the determination of the final diagnosis). We found for CD79a that 9% of centres had a result that was greater than 20%. However, there were 12% of centres that, based upon the CD79a result they obtained (irrespective of whether this was less than or greater than 20%), stated the antigen was deemed to be positive. However, the reverse was true for TdT, where 41% of laboratories had a result of >20% but only 25% stated (irrespective of the result they obtained) that TdT was positive. This indicates that centres are using different approaches to determining when a case is considered positive/negative suggesting the need for greater standardization.

Leukaemia Diagnostic Interpretation - Part Two

This should have been a relatively straightforward diagnosis especially as the molecular genetics were provided. There were 84.2% of returns that correctly classified this as a B lymphoblastic leukaemia/lymphoma with t(v;11q23); MLL rearranged (the consensus Immunophenotyping and molecular genetics were in keeping with this diagnosis). However, as in previous trials there are a significant proportion of laboratories/individuals **that (again) introduce genetic abnormalities that were not provided**. **Again, we stress that doing so means that this is immediately classified as incorrect.** Please read carefully all the data provided and make a conclusion on only the data provided. We will provide **ALL** data relevant to diagnosing a case. Inevitably in some instances there may be other information that is required in order to arrive at a definitive diagnosis in such instances please submit the answer that best fits with the data we have provided. However, we will always provide the correct molecular genetics information where it is available and will not withhold relevant genetics.

Please also note, **only** the consensus immunophenotype provided with Part 2 should be used when considering the final diagnosis. **Do not use the immunophenotype you obtained in Part 1.** This is because if you had an error here you would inevitably introduce an error into your final diagnosis in Part 2. By us providing the consensus phenotype it removes this potential and

means that a laboratory will not be penalised twice because of an error they obtained in Part 1.

EXERCISE CONSENSUS DIAGNOSIS (Classified as Correct)

B lymphoblastic leukaemia/lymphoma with t(v;11q23); MLL rearranged

Other Differential Diagnoses (Classified as Major Errors):

All other diagnoses returned were considered to be incorrect by the Steering Committee because the participating centre or individual introduced either extra molecular genetics information, or there was no supporting immunophenotypic evidence to arrive at the lineage assignment.

For example, 20 returns indicated that this was a mixed phenotype with a t(v;11q23); MLL rearranged. There was no phenotypic indication of another cell lineage being involved. CD15 expression in the absence of other myeloid lineage markers is not considered specific for designation of myeloid lineage involvement. Indeed, its expression on B lymphoid blast cells is a strong indicator of a potential t(v;11q23); MLL rearrangement. Where the return stated specifically that this was AML with t(9;11)(p22;q23);MLLT3-MLL, again there was no evidence of myeloid lineage involvement and as stated above the participants introduced a different MLL translocation that had not been stated or detected.

The 18 returns that classified the case as Acute undifferentiated leukaemia failed to take into account the specific genetic abnormality.

All the other submitted diagnoses are clearly wrong but it should also be noted that there was also no indication that there had been prior cytotoxic therapy to classify this case as a Therapy-related myeloid neoplasm even **IF** this case had a myeloid immunophenotype (which it hasn't).

Other Differential Diagnoses (Classified as Minor Errors):

None

Rationale for Correct Classification

The specific genetic abnormality and the immunophenotype are in keeping with the correct diagnosis.

Further Trial Findings

Table 1: Submissions from all participants - laboratories and individuals.

Diagnosis	Total No. of Returns	No. of Laboratories	No. of Individual
B lymphoblastic leukaemia/lymphoma, with t(v;11q23); MLL rearranged	252	174	77
Mixed phenotype acute leukaemia with t(v;11q23);MLL rearrangement	20	14	6
Acute undifferentiated leukaemia	18	11	7
AML with t(9;11)(p22;q23);MLLT3-MLL	5	3	2
AML without maturation	1	1	0
Lymphocyte-rich classical Hodgkin lymphoma	1	0	1
Therapy-related myeloid neoplasms	1	0	1
B lymphoblastic leukaemia/lymphoma, NOS	1	1	0

Table 2: Submissions from laboratory participants only

Diagnosis	Laboratory Returns %
B lymphoblastic leukaemia/lymphoma, with t(v;11q23); MLL rearranged	85.4
Mixed phenotype acute leukaemia with t(v;11q23);MLL rearrangement	6.8
Acute undifferentiated leukaemia	5.4
AML with t(9;11)(p22;q23);MLLT3-MLL	1.5
AML without maturation	0.5
B lymphoblastic leukaemia/lymphoma, NOS	0.5

Table 3: Submissions from individual participants only

Diagnosis	Individual Returns %
B lymphoblastic leukaemia/lymphoma, with t(v;11q23); MLL rearranged	81.9
Mixed phenotype acute leukaemia with t(v;11q23);MLL rearrangement	6.4
Acute undifferentiated leukaemia	7.4
AML with t(9;11)(p22;q23);MLLT3-MLL	2.1
Lymphocyte-rich classical Hodgkin lymphoma	1.1
Therapy-related myeloid neoplasms	1.1

References:

1. Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine S Jaffe, Stefano A. Pileri, Harald Stein, Jürgen Thiele, James W. Vardiman. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th Edition. IARC Press 2008

Information with respect to compliance with standards BS EN ISO/IEC 17043:2010

4.8.2 a) The proficiency testing provider for this programme is:
UK NEQAS for Leucocyte Immunophenotyping
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4.8.2 b) The coordinators of UK NEQAS LI programmes are Prof David Barnett and Mr Liam Whitby.

4.8.2 c) Person(s) authorizing this report:
Prof David Barnett, Director or Mr Liam Whitby, Operations Manager of UK NEQAS LI

4.8.2 d) No activities in relation to this EQA exercise were subcontracted.

4.8.2 g) The UK NEQAS LI Confidentiality Policy can be found in the Quality Manual which is available by contacting the UK NEQAS LI office. Participant details, their results and their performance data remain confidential unless revealed to the relevant NQAAP when a UK participant is identified as having performance issues.

4.8.2 i) All EQA samples are prepared in accordance with strict Standard Operational Procedures by trained personnel proven to ensure homogeneity and stability. Where appropriate/possible EQA samples are tested prior to issue. Where the sample(s) issued is stabilised blood or platelets, pre and post stability testing will have proved sample suitability prior to issue.

4.8.2 l), n), o), r) & s) Please refer to the UK NEQAS LI website at www.ukneqasli.co.uk for detailed information on each programme including the scoring systems applied to assess performance (for BS EN ISO/IEC 17043:2010 accredited programmes only). Where a scoring system refers to the 'consensus result' this means the result reported by the majority of participants for that trial issue. Advice on the interpretation of statistical analyses and the criteria on which performance is measured is also given. Please note that where different methods/procedures are used by different groups of participants these may be displayed within your report, but the same scoring system is applied to all participants irrespective of method/procedure used.

4.8.2 m) We do not assign values against reference materials or calibrants.

4.8.2 q) Details of the programme designs as authorized by The Steering Committee and Specialist Advisory Group can be found on our website at www.ukneqasli.co.uk. The proposed trial issue schedule for each programme is also available.

4.8.2 t) If you would like to discuss the outcomes of this trial issue, please contact UK NEQAS LI using the contact details provided.